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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	

000570 HM12/0220
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ART UNIT	PAPER NUMBER
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/487,851	LEVY ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The amendment filed on November 30, 2000 has been entered. The examiner assigned to examine the application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1632.

Currently, claims 1-38, 65-68 are under examination, claims 22 and 33 are amended, claim 39 is canceled, claims 65-68 are newly added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-38 remain rejected and claims 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

As recited on the record set forth in Office action dated July 17, 2000, there are many factors to be considered when determining whether the disclosure satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d

1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breath of the claims, and amount of direction provided.

In view the breath of these claims, they read on a method of alleviating *any* (a) disease or disorder in *any* (an) affected animal cell by local delivery to the cell using *any* (a) reverse gene therapy vector encoding *any* (a) "therapeutic gene product which is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder". However, the specification fails to teach one skill in the art to envision what gene products are embraced by the claim language, particularly in the context consistent with the specification. For instance, claim 3 recites some examples of such gene products, such as an apoptosis-inducing protein, or bone morphogenic protein. However, an apoptosis-inducing protein could be a normal cell cycle regulatory protein, and is present in all cells at different levels; the bone morphogenetic proteins (BMPs) constitute a large family of cytokines related to members of the transforming growth factor-beta superfamily and regulate many aspects of vertebrate development including mesoderm patterning, neurogenesis, bone formation, and organogenesis, and are present in normal tissue. These gene products do not meet the criteria set forth in claim 1. The only therapeutic gene product that disclosed in detail in the specification is the mutant HERG protein (A561V), yet, the disclosure of the structure and sequence encoding mutant HERG protein is not disclosed in the specification. Furthermore, the specification teaches to deliver a plasmid encoding a mutant *HERG gene* (a putative K^+ channel gene) to myocytes *in vitro* and *in vivo,* and it also teaches the detection of the

reporter gene expression and the expression of FLAG™ octapeptide (assuming it equals actual mutant HERG protein expression). However, the specification fails to show the expressed protein influenced biophysical function of the K^+ channel in any way in myocytes *in vitro* or in a dog model *in vivo*, and it fails to show the delivered expression vector has any effect on reducing myocardial conductivity in atrila tissue and/or in "alleviating a disease or disorder" of any kind as claims 1-5, 65 read on. The specification does not provide supportive disclosure to enable such generic claims, therefore, it fails to enable one skilled in the art to make and use the invention commensurate with the scope of these claims.

In view the nature of the invention, these claims are drawn to "a method of alleviating a disease or disorder in an affected animal cell" using gene therapy method. In view of the state of the art, and the level of the skill in the art, the record has cited *Eck et al* and *Orkin et al* to summarize the general status of gene therapy art. *Orkin* et al. review the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of

suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). Although the reference is ages old, the general status of gene therapy art has not significantly changed. To illustrate the current status and the unpredictability of gene therapy, the examiner will cite post-filing art as an example, gene therapy for cystic fibrosis (CF). CF is a single gene defective, inherited disease and the attempt in CF gene therapy has been the pioneer in the field. *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) review status of gene therapy for cystic fibrosis lung disease. "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." *Boucher* et al further teach obstacles researchers faced --the target cell should be small airways, because they are the first and major obstruction in pulmonary functional abnormality, however, these cells are very difficult to reach; --the effectiveness of gene delivery, difficulties in achieving a low level persistent expression per cell in virtually every affected cell. Obviously, gene therapy is such a complicated art, merely having a known defective gene, merely delivering an expression vector to a local target tissue does NOT equal achieving a therapeutic effect. The teachings of *Boucher et al* fully illustrate the unpredictability of gene therapy in general.

The specification recites many candidate genes that asserted to be useful for "reverse gene therapy". However, for some of the recited genes, the art of record has shown the lack of enablement to use for gene therapy, or the art teaches away from the instant specification. For example, claim 3 recites "the protein is selected from the group consisting of ..., an apoptosis-inducing protein..." and the specification teaches: "e.g. delivery of an apoptosis-inducing gene to myocardium cells which form all or part of conduction pathway associated with arrhythmia." (page 16, lines 27-30) Mutant p53 gene is a known as one of the cancer-associated genes, delivery of wild-type p53 gene will theoretically induce apoptosis and inhibit tumor growth. *Vinyals et al* (Gene Ther 1999 Jan; 6:22-33) teach "THE INTRODUCTION OF EXOGENOUS WILD-TYPE P53 INTO HUMAN CANCER CELLS BEARING P53 MUTATION DOES NOT NECESSARILY RESULT IN INHIBITION OF TUMOR GROWTH." They teach that most wtp 53-expressing cells died by apoptosis at early stage, but they did obtain 3 colonies with wtp 53 expression out of six clones selected *in vitro*. When these three clones were implanted orthotopically in nude mice, only one clone showed prolonged tumor latency, yet "NO DIFFERENCES WERE FOUND IN EITHER TUMOR PROLIFERATION OR APOPTOSIS IN TUMORS.(...) THE PRESENCE OF MUTATED P53 MAY CONFER GENOME INSTABILITY AND MUTATOR ABILITY, WHICH ALLOWS CELLS TO ESCAPE THE EFFECTS OF THE EXOGENOUS WTP 53 AND CONTRIBUTES TO THE FAILURE OF WTP53 GENE THERAPY." For another example, claim 20 recites "wherein the reverse gene therapy vector further comprises a Cre-recombinase-sensitive site", and the specification teaches: "Expression of a gene product encoded by the gene therapy vector described herein can be rendered terminable by incorporating a Cre-recombinase sensitive site in the nucleic acid of the

gene therapy vector (Hammond et al., 1997...)" (page 15, lines 17-20). *Okuyama T et al* (Gene Ther 1998 Aug; 8:1047-53) teach using a Cre-mediated switching system for delivering Fas-ligand (AxCALNFFasL, an apoptosis-inducing gene) to induce apoptosis in rodent liver. They teach "OUR INITIAL ATTEMPT TO CONSTRUCT AN E1/E3-DELETED ADENOVIRUS EXPRESSING RAT FAS-LIGHAND UNDER THE CONTROL OF THE CAG PROMONTER WAS UNSUCCESSFUL, BECAUSE THE TRANSFECTED 293 CELLS RAPIDLY INDUCED APOPTOSIS", they teach to construct a Cre-mediated switching system to turn on the FasL expression; they teach "COS-7 CELLS INFECTED WITH AXCALNFFASL ALONE DID NOT INDUCE APOPTOSIS IN COCULTIVATED JURKAT CELLS, BUT THE CELLS TREATED WITH AXCALNFFASL AND AXCANCRE (AN ADENOVIRUS EXPRESSING CRE RECOMBINASE WITH THE CAG PROMOTER) DID." Both *Okuyama T et al* and *Vinyals et al* teach simply using "a vector encoding an apoptosis-inducing protein operatively linked to a promoter" will not be successful in achieving the gene therapy effect as theoretically assumed. *Okuyama T et al* also demonstrate an opposite effect from the teaching of this specification for using Cre-recombinase. The teachings of *Okuyama T et al Vinyals et al* render the lack of enablement for the instantly claimed apoptosis-inducing protein as well as demonstrate the unpredictability of the gene therapy art. Apparently, simply listing candidate genes and potential targeting diseases in the specification does NOT enable instant claims. Without painstaking experimentation, applicants are not entitled to claim alleviating any disease in any cell using the recited genes, because without undue experimentation, one of skill in the art could not make and use the invention as broadly claimed.

More specifically, one preferred embodiment of the instant application is mutant HERG protein. In view of the state of the art and the level of knowledge to *HERG*, apparently it is known that *HERG* gene encodes a cardiac K+ channel with six transmembrane segments, and certain form of HERG gene mutation is related to Long QT syndrome possibly due to abnormal k+ channel function. The specification asserts: "*Because both ibutilide and defective HERG protein inhibit K^+ current through the HERG membrane protein, administration of defective HERG portion to a patient afflicted with re-entrant atrial flutter using a reverse gene therapy method as described herein will relieve this condition.*"(page 12, line17-23) However, it is noted that there are many other forms of K+ channel coding genes, and the function of HERG is not as straightforward as asserted in the specification. *Sanguinetti et al* (IDS) teach "INTERESTINGLY, HERG CURRENT IS NOT BLOCKED BY DRUGS THAT SPECIFICALLY BLOCK I_{KR} IN CARDIAC MYOCYTES. THESE DATA INDICATE THAT HERG PROTEINS FORM I_{KR} CHANNELS, BUT THAT AN ADDITIONAL SUBUNIT MAY BE REQUIRED FOR DRUG SENSITIVTY."(Abstract) Please also note, the etiology and mechanism of re-entrant atrial flutter is not fully understood in the art, and most often seen in persons with organic heart disease or after open-heart surgery, whereas a mutant *HERG* gene is only one of the K+ channel coding genes, a cause for Long QT syndrome, an autosomal dominant inherited disease having completely different etiology and mechanism compared with re-entrant atrial flutter. In light of the teaching of *Kagan et al, Sanguinetti et al*, even though it has been shown that a expressed HERG are nearly identical to the rapidly activating delayed rectifier K^+ current in cardiac myocytes, the biophysical effect of the expressed mutant HERG

fusion protein on the re-entrant atrial flutter dog model is yet to be determined, in other words, the effect of mutant HERG on the dog model of re-entrant atrial flutter is not predictable until the actual effect is shown. Given the nature of the *HERG* gene, the nature of the re-entrant flutter, the level of those skill in the art, the unpredictability of HERG protein effect, and the unpredictability of the gene therapy art, the examiner has provided reasonable basis to raise the question to the enablement disclosure of the instant specification. In absence of evidence to the contrary, and in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation commensurate with these claims.

In addition, claims 2-5, 35, 36, 66 recite a defective *HERG* gene product encoded by an expression vector. The disclosure to this critical embodiment of the invention is relied upon a reference to non-patent prior arts, improperly incorporated the subject matter into this application. Paragraph bridging pages 11 and 12 recites many references, it is not clear which reference disclosed the detailed structure and sequence of the vector which used in the instant specification. One skill in art could not practice the invention without a proper disclosure of this particular embodiment.

Applicant's arguments filed November 30, 2000 have been fully considered but they are not persuasive.

THE RELEVANCE OF KNOWN INVENTIVE ELEMENTS AND THE ENABLEMENT OF CLAIMED EFFECT

In paragraphs spinning from page 3 to page 5 of the amendment, the applicants attorney basically argue that the examiner has no reason to challenge the enablement disclosure of the specification. The examiner disagrees with the argument for the reason set forth in the previous office action and this office action.

The concerned issue is not about whether certain embodiment of the invention is optimized, or whether one skill in the art knows of how to make an expression vector, but to remind the applicants that simply making and delivering an expression vector is not equivalent to achieving a desired therapeutic effect as required by the claims. The amendment reads "*the elements recited in the claim are i) a cell affected with a disease or disorder, ii) a gene therapy vector, iii) a promoter, and iv) a nucleic acid encoding a therapeutic gene product...*" "*The Applicant respectfully contend that each of these elements is known to the skilled artisan, and that once the skilled artisan is told that these elements should be combined in the manner set forth in the specification, the skilled artisan would not have any difficulty doing so.*" (page 4, line 2-5) If the assertion is factually accurate, the applicants, as skilled artisans, have possessed all the elements needed to practice the invention, have delivered the expression vector locally, therefore, should be able to and are required by the MPEP to disclose each aspect of the claimed invention, to demonstrate the biophysical effect of the expressed mutant HERG on myocardial conductivity in the dog model, to minimally show a reduced inducibility of the re-entrant atrial flutter as they disclosed in figure 1 for Ibutilide

controlled release matrices. However, the specification fails to demonstrate that merely delivering the vector encoding HERG (A561V) achieved any therapeutic effect.

REGARDING THERAPEUTIC ASPECT OF THE CLAIMS

In paragraphs beginning with "Third" and Fourth" on page 6, the attorney argues that no "therapeutic levels" have been recited in any pending claim. However, it is advised that for claims such as " a method for alleviating a disease", "the therapeutic gene product", "gene therapy vector" "medicament", are interpreted as a therapeutic agent or method by the Office, subsequently they are required to show a therapeutic effect. The basis of such practice is MPEP 2164.01 (c): "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE." The instant method claims recite the use "for alleviating a disease" therein, the enablement relative to the use has to be evaluated.

The attorney further states that "*It is sufficient to achieve only transient, low-level expression of a therapeutic gene, at least for certain disease and disorders, as would be understood by the skilled artisan*". However, applicants provide no evidence to support this assertion. The example of gene therapy for CF has indicated that a local delivery of CFTR does not result in a therapeutic effect, and the expression of wide type p53 has not been able to suppress tumor growth *in vivo*. *Eck et al* explain that numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Among those are the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell

population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. (Eck et al., bridging pages 81-82) Therefore, it is reasonable for any one skilled in the art to raise a doubt that a transient, low-level delivery of the therapeutic genes listed in the claims will achieve disease-alleviating effect in the absence of the evidence to the contrary.

REQUIREMENT FOR ENABLING DISCLOSURE

In paragraphs on page 7, the focus of the argument is that "*The Applicants ...are not required to prove to the Examiner that the claimed invention is enabled.*" (page 7, paragraph 3). The statement is contradicting the MPEP.

According to MPEP as pursuant to an enabling disclosure required by 35 U.S.C 112, first paragraph,

"AN APPLICANT'S SPECIFICATION MUST ENABLE A PERSON SKILLED IN THE ART TO MAKE AND USE THE CLAIMED INVENTION WITHOUT UNDUE EXPERIMENTATION.(...) AS SUCH, THE DISCLOSURE MUST TEACH A PERSON SKILLED IN EACH ART HOW TO MAKE AND USE THE RELEVANT ASPECT OF THE INVENTION WITHOUT *UNDUE* EXPERIMENTATION. FOR EXAMPLE, TO ENABLE A CLAIM TO A PROGRAMMED COMPUTER THAT DETERMINES AND DISPLAYS THE THREE-DIMENSIONAL STRUCTURE OF A CHEMICAL COMPOUND, THE DISCLOSURE MUST

- ENABLE A PERSON SKILLED IN THE ART OF MOLECULAR MODELING TO UNDERSTAND AND PRACTICE THE UNDERLYING MOLECULAR MODELING PROCESSES; AND
- ENABLE A PERSON SKILLED IN THE ART OF COMPUTER PROGRAMMING TO CREATE A PROGRAM THAT DIRECTS A COMPUTER TO CREATE AND DISPLAY THE IMAGE REPRESENTING THE THREE-DIMENSIONAL STRUCTURE OF THE COMPOUND.

IN OTHER WORDS, THE DISCLOSURE CORRESPONDING TO EACH ASPECT OF THE INVENTION MUST BE ENABLING TO A PERSON SKILLED IN EACH RESPECTIVE ART. (MPEP 2106.B.2)

For the reasons of record and those set forth above, the instant specification fails to meet the enablment requirement.

Claim 1-38, 65-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites " a method of alleviating a disease or disorder in an affected animal cell". However, a disease is "A CONDITION OF THE LIVING ANIMAL OR PLANT BODY OR OF ONE OF ITS PARTS THAT IMPAIRS NORMAL FUNCTIONING." A cell could be a cultured cell such as those in cultivated tumor cell lines. It is vague and indefinite to claim alleviating a disease in a cell.

These claims are vague and indefinite because the term "reverse" in these claims and specification is used to mean "undesirable," (page 8, line 21). However, the accepted meaning in an English dictionary is "ACTING, OPERATING, OR ARRANGED IN A MANNER CONTRARY TO THE USUAL" among many of the similar explanations. In view of the definition for gene therapy, *Eck et al* teach "IN INHERITED DISORDERS, A SINGLE DEFECTIVE GENE THAT CAUSES THE DISORDER TYPICALLY IS THE SUBJECT OF INTERVENTION. BY CONTRAST, IN ACQUIRED DISEASES, EITHER A DEFECTIVE GENE THAT DIRECTLY CONTRIBUTES TO THE DISORDER, OR A GENE THAT MEDIATE AN UNRELATED BIOCHEMICAL PROCESS, MAY BE THE BASIS FOR INTERVENTION." (the last paragraph in page 78) The concept of the "reverse gene therapy" presented in the specification is embraced by this teaching in gene therapy for acquired disease. The recited reverse gene therapy vectors, the method of release, the

locally delivery manner, the candidate genes are not "acting, operating, or arranged in a manner contrary to the usual" i.e. those used in "desired" gene therapy.

Claims 1 recites "a therapeutic gene product which is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder", The terms "abnormal", "usually", and "not afflicted" are not defined. There are no common structure or functions among claim recited gene products. Consequently, the metes and bounds of the "therapeutic gene product" are unclear.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the other examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:00 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Q. Janice Li
Examiner
Art Unit 1632

QJL
February 15, 2001

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER